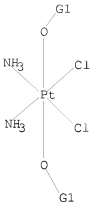
```
chain nodes :
1  2  3  4  5  6  7  9  10
chain bonds :
1-2  1-3  1-4  1-5  1-6  1-7  6-9  7-10
exact/norm bonds :
6-9  7-10
exact bonds :
1-2  1-3  1-4  1-5  1-6  1-7


G1:Ca,K,Li,Mg,Na,Cb,Ak

Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  9:CLASS  10:CLASS



L1      STRUCTURE UPLOADED

=> d his

     (FILE 'HOME' ENTERED AT 18:44:21 ON 05 MAY 2008)

     FILE 'REGISTRY' ENTERED AT 18:44:35 ON 05 MAY 2008
L1              STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
```




G1 Ca,K,Li,Mg,Na,Cb,Ak

Structure attributes must be viewed using STN Express query preparation.

```
=> s l1
SAMPLE SEARCH INITIATED 18:44:56 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      166 TO ITERATE

100.0% PROCESSED      166 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         2547 TO     4093
PROJECTED ANSWERS:               3 TO      162

L2            3 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 18:45:02 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     2996 TO ITERATE

100.0% PROCESSED     2996 ITERATIONS                               68 ANSWERS
SEARCH TIME: 00.00.01

L3           68 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                  178.36     178.57

FILE 'CAPLUS' ENTERED AT 18:45:09 ON 05 MAY 2008
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 5 May 2008 VOL 148 ISS 19
FILE LAST UPDATED: 4 May 2008 (20080504/ED)



=> s l3
L4 22 L3

=> d 1-22 bib abs

L4 ANSWER 1 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1373074 CAPLUS
DN 148:181734
TI Novel Di- and Tetracarboxylatoplatinum(IV) Complexes. Synthesis, Characterization, Cytotoxic Activity, and DNA Platination
AU Reithofer, Michael R.; Valiahdi, Seied M.; Jakupec, Michael A.; Arion, Vladimir B.; Egger, Alexander; Galanski, Markus; Keppler, Bernhard K.
CS Institute of Inorganic Chemistry, University of Vienna, Vienna, A-1090, Austria
SO Journal of Medicinal Chemistry (2007), 50(26), 6692-6699
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 148:181734
AB Octahedrally configured diaminedichloro- and diamineoxalatoplatinum(IV) complexes with axial hydroxo ligands were carboxylated with succinic or glutaric anhydride. The free, uncoordinated carboxylic acid groups were further derivatized with amines and alcs. to the resp. amides and esters and characterized in detail by elemental anal., mass spectrometry, and multinuclear (1H, 13C, 15N, and 195Pt) NMR spectroscopy. Cytotoxicity of the complexes was studied in four human cancer cell lines derived from ovarian carcinoma (CH1, SK-OV-3), cervical carcinoma (HeLa), and colon carcinoma (SW480) by the MTT assay. Structure-activity relations revealed a low activity for Pt complexes with underivatized carboxylic acid moieties and amide derivs. displaying the hydroxyethylamino residue. Within amides, cyclopentylamino analogs were equipped with the highest cytotoxic potential. However, ester derivs. yielded IC50 values mostly in the low micromolar range and comparable to those of cisplatin. DNA platination studies of selected complexes revealed a high DNA platination capacity in parallel to a high cytotoxic potential and vice versa.

L4 ANSWER 2 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1203726 CAPLUS
DN 148:23931
TI Reduction of cis,trans,cis-[PtCl2(OCOCH3)2(NH3)2] by Aqueous Extracts of Cancer Cells
AU Nemirovski, Alina; Kasherman, Yonit; Tzaraf, Yael; Gibson, Dan
CS Department of Medicinal Chemistry and Natural Products, School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, 91120, Israel
SO Journal of Medicinal Chemistry (2007), 50(23), 5554-5556
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal

LA English
AB Pt(IV) complexes must be reduced to kill cancer cells. While reduction rates correlate with reduction potentials, we wanted to check if the rates of reduction
depend on the cell line used. The reduction of cis,trans,cis-[PtCl2(OCOCH3)2(NH3)2] by exts. of three cell lines was measured, and the rates follow the order A2780cisR > A2780 > HT-29. The reduction is not carried out by the low mol. weight (MW) antioxidants but primarily by cellular components with MW > 3000.
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1080753 CAPLUS
DN 147:527837
TI Calculation of Lipophilicity of a Large, Diverse Dataset of Anticancer Platinum Complexes and the Relation to Cellular Uptake
AU Oldfield, Steven P.; Hall, Matthew D.; Platts, James A.
CS School of Chemistry, Cardiff University, Cardiff, CF10 3AT, UK
SO Journal of Medicinal Chemistry (2007), 50(21), 5227-5237
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB A quant. structure-property relationship (QPSR) for the octanol-water partition of platinum complexes was constructed using mol. descriptors derived from d. functional (DFT) calcns. A dataset of partition data for 64 complexes, consisting of 43 square-planar platinum(II) and 21 octahedral platinum(IV) complexes, was drawn from literature sources. Not only does this dataset include considerable structural diversity of complexes considered but also a variety of techniques for the measurement of partition coeffs. These data were modeled using descriptors drawn from electrostatic potentials and hardness/softness indexes projected onto mol. surfaces. This required initial descriptor selection using a genetic algorithm approach, followed by partial least-squares regression against log Po/w data. In this way, a statistically robust model was constructed, with errors of similar size to the variation in log Po/w from multiple exptl. measurements. Implications of lipophilicity for cellular accumulation of Pt-based drugs, and hence for design of new drugs, are discussed, as is the uptake of metabolites of cisplatin.
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1012725 CAPLUS
DN 148:85278
TI Conjugated Platinum(IV)-Peptide Complexes for Targeting Angiogenic Tumor Vasculature
AU Mukhopadhyay, Sumitra; Barnes, Carmen M.; Haskel, Ariel; Short, Sarah M.; Barnes, Katie R.; Lippard, Stephen J.
CS Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SO Bioconjugate Chemistry (2008), 19(1), 39-49
CODEN: BCCHES; ISSN: 1043-1802
PB American Chemical Society
DT Journal
LA English
AB The integrins $\alpha v\beta 3$ and $\alpha v\beta 5$ and the membrane-spanning surface protein aminopeptidase N (APN) are highly expressed in tumor-induced angiogenesis, making them attractive targets for therapeutic intervention. Both integrins and APN recognize a broad range of peptides containing RGD (Arg-Gly-Asp) and NGR (Asn-Gly-Arg) motifs,

resp. Here, we describe the design, synthesis, and characterization of a series of mono- and difunctionalized platinum(IV) complexes in which a conjugated peptide motif, containing RGD, (CRGDC)c, (RGDfK)c, or NGR, is appended as a "tumor-homing device" to target tumor endothelial cells selectively over healthy cells. Platinum(IV)-peptide complexes with nonspecific amino acids or peptide moieties were prepared as controls. Concentration-response curves of these compds. were evaluated against primary proliferating endothelial cells and tumor cell lines and compared to those of cisplatin, a well-described platinum-based chemotherapeutic agent. The Pt(IV)-RGD conjugates were highly and specifically cytotoxic to cell lines containing $\alpha v\beta 3$ and $\alpha v\beta 5$, approaching the activity of cisplatin. The Pt(IV)-NGR complexes were less active than Pt(IV)-RGD-containing compds. but more active than nonspecific Pt-peptide controls. Integrin $\alpha v\beta 3$ mediated, at least in part, the anti-proliferative effect of a Pt(IV)-RGD conjugate, as demonstrated by a decreased inhibitory response when endothelial cells were either (1) incubated with an excess of $\alpha v\beta 3/\alpha v\beta 5$-specific RGD pentapeptides or (2) transfected with RNAi for $\beta 3$, but not $\beta 1$, integrins. These results suggest a rational approach to improved chemotherapy with Pt(IV)-peptide conjugates by selective drug delivery to the tumor compartment.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:646516 CAPLUS
DN 147:242935
TI Soluble Single-Walled Carbon Nanotubes as Longboat Delivery Systems for Platinum(IV) Anticancer Drug Design
AU Feazell, Rodney P.; Nakayama-Ratchford, Nozomi; Dai, Hongjie; Lippard, Stephen J.
CS Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SO Journal of the American Chemical Society (2007), 129(27), 8438-8439
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Amine-functionalized soluble single-walled carbon nanotubes (SWNTs) were derivatized with cisplatin prodrug conjugates as a delivery system by which to internalize multiple prodrug centers. The platinum(IV) complex, c,c,t-[Pt(NH3)2Cl2(OEt)(O2CCH2CH2CO2H)], was tethered to the surface of the carbon nanotubes through peptide linkages formed by the reaction of the SWNT-tethered amines with the carboxylate moiety. The SWNTs were taken into testicular cancer cells by endocytosis, where the drop in pH facilitates reductive release of the platinum(II) core complex, which then readily diffuses throughout the cell, as determined by platinum atomic absorption spectroscopy. The entrapment of the SWNTs within the endosomes was confirmed by fluorescence microscopy of SWNTs containing both tethered fluorescein and platinum units. The cytotoxicity of the free platinum(IV) complex increases by >100-fold when the complex is attached to the surface of the functionalized SWNTs.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:599431 CAPLUS
DN 146:324
TI The fate of platinum(II) and platinum(IV) anti-cancer agents in cancer cells and tumors
AU Hall, Matthew D.; Alderden, Rebecca A.; Zhang, Mei; Beale, Philip J.; Cai,

Zhonghou; Lai, Barry; Stampfl, Anton P. J.; Hambley, Trevor W.
CS Centre for Heavy Metals Research, School of Chemistry F11, The University of Sydney, NSW 2006, Australia
SO Journal of Structural Biology (2006), 155(1), 38-44
CODEN: JSBIEM; ISSN: 1047-8477
PB Elsevier
DT Journal
LA English
AB SRIXE mapping has been used to gain insight into the fate of platinum(II) and platinum(IV) complexes in cells and tumors treated with anticancer active complexes to facilitate the development of improved drugs. SRIXE maps were collected of thin sections of human ovarian (A2780) cancer cells treated with bromine containing platinum complexes, cis-[PtCl2(3-Brpyr)(NH3)] (3-Brpyr = 3-bromopyridine) and cis,trans,cis-[PtCl2(OAcBr)2(NH3)2] (OAcBr = bromoacetate), or a platinum complex with an intercalator attached cis-[PtCl2(2-[(3-aminopropyl)amino]-9,10-anthracenedione)(NH3)]. After 24 h the complexes appear to be localized in the cell nucleus with a lower concentration in the surrounding cytoplasm. In cells treated with cis-[PtCl2(3-Brpyr)(NH3)] the concentration of bromine was substantially higher than in control cells and the bromine was co-localized with the platinum consistent with the 3-bromopyridine ligand remaining bound to the platinum. The cells treated with cis,trans,cis-[PtCl2(OAcBr)2(NH3)2] also showed an increased level of bromine, but to a much lesser extent than for those treated with cis-[PtCl2(3-Brpyr)(NH3)] suggestive of substantial reduction of the platinum(IV) complex. Maps were also collected from thin sections of a 4T1.2 neo 1 mammary tumor xenograft removed from a mouse 3 h after treatment with cis,trans,cis-[PtCl2(OH)2(NH3)2] and revealed selective uptake of platinum by one cell.
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1163378 CAPLUS
DN 144:63383
TI Synthesis and Characterization of Platinum(IV) Anticancer Drugs with Functionalized Aromatic Carboxylate Ligands: Influence of the Ligands on Drug Efficacies and Uptake
AU Ang, Wee Han; Pilet, Sebastien; Scopelliti, Rosario; Bussy, Francois; Juillerat-Jeanneret, Lucienne; Dyson, Paul J.
CS Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), Lausanne, CH 1015, Switz.
SO Journal of Medicinal Chemistry (2005), 48(25), 8060-8069
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 144:63383
AB Trans-Pt(IV) complexes with functionalized aromatic carboxylate ligands, cis,cis,trans-Pt(NH3)2Cl2(CO2C6H4R)2 (R = H (3), p-vinyl (4), p-methoxy (5), p-iodo (6), p-cyano (7), or o-carboxyl (8)) was synthesized and characterized by spectroscopic methods. Crystal structures of 3, 4, 7, and 8 were obtained, which revealed that their structural conformations were influenced by intramol. H-bonding interactions. The complexes were evaluated for cellular uptake and inhibition of cell proliferation against a panel of lung, colon, and breast carcinoma cell lines. The functionalization of the aromatic carboxylate ligand has a profound influence on the uptake, and hence, efficacy, of this class of complex.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:1014223 CAPLUS

DN 143:359627
TI The influence of tumor microenvironmental factors on the efficacy of cisplatin and novel platinum(IV) complexes
AU Mellor, H. R.; Snelling, S.; Hall, M. D.; Modok, S.; Jaffar, M.; Hambley, T. W.; Callaghan, R.
CS Oxford Drug Resistance Group, Nuffield Department of Clinical Laboratory Sciences, John Radcliffe Hospital, University of Oxford, Oxford, OX3 9DU, UK
SO Biochemical Pharmacology (2005), 70(8), 1137-1146
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier B.V.
DT Journal
LA English
AB The chemotherapeutic drug cisplatin is an important treatment for many types of solid tumors, in particular non-small cell lung cancer (NSCLC). Platinum(IV) complexes offer several advantages to cisplatin due to their requirement for reduction to the active platinum(II) form to elicit cytotoxicity. This should minimize non-specific effects and facilitate higher amts. of the active complexes reaching the target DNA. Hypoxia and a quiescent cell population are features of the tumor microenvironment known to lead to resistance to many chemotherapeutic agents. It is unclear how these microenvironmental factors will impact on the efficacy of novel platinum(IV) complexes. Consequently, the cytotoxicities of several platinum drugs were determined in monolayer and tumor spheroid cultures derived from NSCLC lines. Platinum(IV) reduction potential correlated well with cytotoxicity. The complex containing a chloro axial ligand demonstrated the greatest potency and the drug with the hydroxy ligand was the least effective. Although drug cytotoxicity was not enhanced under hypoxic conditions, both cisplatin and the platinum(IV) complexes retained full potency. In addition, all of the platinum drugs retained the ability to evoke apoptosis in quiescent cells. In summary, unlike many anticancer drugs, the platinum(IV) complexes retain cytotoxic potency under resistance-inducing tumor microenvironmental conditions and warrant further investigation as more selective alternatives to current platinum-based therapy for the treatment of solid tumors.
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:395221 CAPLUS
DN 142:441848
TI Method for the preparation of trans- or cis-diammoniumdichlorodihydroxoplatinum (IV), and use for the treatment of cancer
IN Salama, Zoser B.
PA Germany
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2005040045 | A2 | 20050506 | WO 2004-DE2296 | 20041013 |
| | WO 2005040045 | A3 | 20050707 | | |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| | RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, | | | | |

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1524273 A1 20050420 EP 2003-90344 20031013
EP 1524273 B1 20061122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
AU 2004283125 A1 20050506 AU 2004-283125 20041013
CA 2565096 A1 20050506 CA 2004-2565096 20041013
EP 1678189 A2 20060712 EP 2004-789998 20041013
EP 1678189 B1 20070321
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK
CN 1867573 A 20061122 CN 2004-80029889 20041013
BR 2004015295 A 20061226 BR 2004-15295 20041013
JP 2007513066 T 20070524 JP 2006-534580 20041013
MX 2006PA03843 A 20070202 MX 2006-PA3843 20060406
IN 2006DN02642 A 20070810 IN 2006-DN2642 20060511
US 20070286905 A1 20071213 US 2007-595400 20070202
PRAI EP 2003-90344 A 20031013
US 2003-512097P P 20031020
WO 2004-DE2296 W 20041013
OS MARPAT 142:441848
AB The invention relates to a method for the production of trans- or cis-diammoniumdichlorodihydroxoplatinum (IV) and derivs. thereof. Trans- or cis-diammoniumdichloroplatinum (II) is reacted with a solution containing >30% peroxide at temps. below 30°C, the product obtained thereby is dissolved with a mineral acid and finally precipitated with an alkaline solution The compds. of the invention are useful as therapeutic agents for the treatment of e.g. cancer.

L4 ANSWER 10 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:31552 CAPLUS
DN 142:273345
TI Rational Design of Platinum(IV) Compounds to Overcome Glutathione-S-Transferase Mediated Drug Resistance
AU Ang, Wee Han; Khalaila, Isam; Allardyce, Claire S.; Juillerat-Jeanneret, Lucienne; Dyson, Paul J.
CS Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne EPFL-BCH, Lausanne, CH 1015, Switz.
SO Journal of the American Chemical Society (2005), 127(5), 1382-1383
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB A rationally designed Pt(IV) anticancer compound is described, employing the novel concept of tethering an inhibitor of glutathione-S-transferase, an enzyme associated with Pt-based drug-resistance, to cisplatin. Its enzyme inhibition activity, investigated using spectrophotometric and mass spectrometry-based techniques, and cytotoxic profile in resistant cancer cells are described.
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

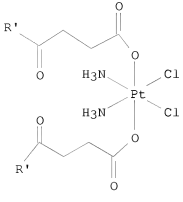
L4 ANSWER 11 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:1019754 CAPLUS
DN 141:419813
TI Coordination complexes having tethered therapeutic agents and/or targeting moieties, and methods of making and using the same
IN Lippard, Stephen J.; Barnes, Carmen M.; Haskel, Ariel; Barnes, Katie R.

PA Massachusetts Institute of Technology, USA
SO U.S. Pat. Appl. Publ., 63 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

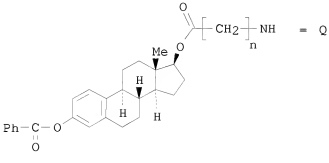
| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 20040235712 | A1 | 20041125 | US 2004-755855 | 20040112 |
| | US 7138520 | B2 | 20061121 | | |
| PRAI | US 2003-439729P | P | 20030113 | | |
| | US 2003-505088P | P | 20030923 | | |

OS MARPAT 141:419813
GI

I



II



AB In part, the present invention is directed to coordination complexes comprising a therapeutic agent. Claimed is a compound comprising: (a) a Pt metal center (b) two cis labile ligands bonded to the Pt, and (c) one or more therapeutic agents and/or targeting moieties covalently attached to the Pt, wherein the therapeutic agent is not covalently attached to the Pt center through the cis labile ligands. The two cis labile ligands may be halides, the therapeutic agent may be a steroid, e.g., estrogen, and the targeting moiety may be a peptide. The compds. include cis,cis,trans complexes I (X = labile covalently bonded ligand, or X2 = bidentate ligand; L = ligand covalently bonded to Pt center, or L2 = bidentate ligand; M = therapeutic agent, targeting moiety, or labile covalently bonded ligand; R = therapeutic agent or targeting moiety). Example complexes prepared are cisplatin derivs. II (R' = Q, n = 1-5) containing estradiol-3-benzoate tethered to the Pt and peptide-tethered derivs. II (R' = peptide, e.g., NGRNH-, AGRNH-, and biotin-labeled derivs.). Reduction of the Pt(IV) complexes to Pt(II) releases the therapeutic agent or targeting moiety to be therapeutically effective for treatment of cancer cells which comprise a receptor for the agent/moiety, especially where the

therapeutic agent causes increased expression of HMG or the cancer cells express estrogen ER(+) receptors. Cytotoxicities of compds. II against MCF-7 and HCC-1937 cell lines were studied. Also claimed is a kit comprising the compds. and instructions for administering the compound to a patient.

RE.CNT 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:819575 CAPLUS
DN 142:361
TI The mechanism of action of platinum(IV) complexes in ovarian cancer cell lines
AU Hall, Matthew D.; Amjadi, Shahriar; Zhang, Mei; Beale, Philip J.; Hambley, Trevor W.
CS Centre for Heavy Metals Research, School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia
SO Journal of Inorganic Biochemistry (2004), 98(10), 1614-1624
CODEN: JIBIDJ; ISSN: 0162-0134
PB Elsevier B.V.
DT Journal
LA English
AB The reduction potentials, lipophilicities, cellular uptake and cytotoxicity have been examined for two series of platinum(IV) complexes that yield common platinum(II) complexes on reduction: cis-[PtCl4(NH3)2], cis,trans,cis-[PtCl2(OAc)2(NH3)2], cis,trans,cis-[PtCl2(OH)2(NH3)2], [PtCl4(en)], cis,trans-[PtCl2(OAc)2(en)] and cis,trans-[PtCl2(OH)2(en)] (en = ethane-1,2-diamine, OAc = acetate). As previously reported, the reduction occurs most readily when the axial ligand is chloride and least readily when it is hydroxide. The en series of complexes are marginally more lipophilic than their ammine analogs. The presence of axial chloride or acetate ligands results in a slighter higher lipophilicity compared with the platinum(II) analog whereas hydroxide ligands lead to a substantially lower lipophilicity. The cellular uptake is similar for the platinum(II) species and their analogous tetrachloro complexes, but is substantially lower for the acetato and hydroxo complexes, resulting in a correlation with the reduction potential. The activities are also correlated with the reduction potentials with the tetrachloro- complexes being the most active of the platinum(IV) series and the hydroxo- complexes being the least active. These results are interpreted in terms of reduction, followed by aquation reducing the amount of efflux from the cells resulting in an increase in net uptake.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:324513 CAPLUS
DN 140:385646
TI Synthesis, Characterization, and Cytotoxicity of a Series of Estrogen-Tethered Platinum(IV) Complexes
AU Barnes, Katie R.; Kutikov, Alexander; Lippard, Stephen J.
CS Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SO Chemistry & Biology (2004), 11(4), 557-564
CODEN: CBOLE2; ISSN: 1074-5521
PB Cell Press
DT Journal
LA English
OS CASREACT 140:385646
AB Several estrogen-tethered platinum(IV) complexes were prepared and characterized by ESI-MS and 1H NMR spectroscopy. Their design was inspired by the observation that estrogen receptor-pos. cells exposed to

the hormone are sensitized to cisplatin. Intracellular reduction of bis-estrogen-cis-diamminedichloroplatinum(IV), BEPn (where n = 1-5 methylene groups between Pt and estrogen), occurs to afford cisplatin and two equivalent of the linker-modified estrogen. The ability of BEPn to induce overexpression of HMGB1 was established by immunofluorescence microscopy. The cytotoxicity of the compds. was evaluated in ER(+) MCF-7 and ER(-) HCC-1937 human breast cancer cell lines. BEP3 selectively induces overexpression of HMGB1 in MCF-7 cells, compared to HCC-1937 cells, and enhances their sensitivity (IC50 = 2.1±0.4 μM vs. 3.7±0.9 μM, resp.) to the compound The difference in compound activities and the potential of compds. of this class for treating breast and ovarian cancer are discussed.

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:726129 CAPLUS
DN 140:192358
TI The cellular distribution and oxidation state of platinum(II) and platinum(IV) antitumour complexes in cancer cells
AU Hall, Matthew D.; Dillon, Carolyn T.; Zhang, Mei; Beale, Philip; Cai, Zhonghou; Lai, Barry; Stampfl, Anton P. J.; Hambley, Trevor W.
CS School of Chemistry F11, Centre for Heavy Metals Research, The University of Sydney, 2006, Australia
SO JBIC, Journal of Biological Inorganic Chemistry (2003), 8(7), 726-732
CODEN: JJBCFA; ISSN: 0949-8257
PB Springer-Verlag
DT Journal
LA English
AB The cellular distribution of platinum in A2780 ovarian cancer cells treated with cisplatin and platinum(IV) complexes with a range of reduction potentials has been examined using elemental anal. (synchrotron radiation-induced x-ray emission). The cellular distribution of platinum(IV) drugs after 24 h is similar to that of cisplatin, consistent with the majority of administered platinum(IV) drugs being reduced. Micro-x-ray absorption near-edge spectra of cells treated with cisplatin and platinum(IV) complexes confirmed the reduction of platinum(IV) to platinum(II). In cells treated, the most difficult to reduce complex, cis,trans,cis-[PtCl2(OH)2(NH3)2], platinum(IV) was detected in the cells along with platinum(II). The observations are in accordance with the relative ease of reduction of the platinum(IV) complexes used and support the requirement of reduction for activation of platinum(IV) complexes.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:415965 CAPLUS
DN 139:111256
TI XANES Determination of the Platinum Oxidation State Distribution in Cancer Cells Treated with Platinum(IV) Anticancer Agents
AU Hall, Matthew D.; Foran, Garry J.; Zhang, Mei; Beale, Philip J.; Hambley, Trevor W.
CS Centre for Heavy Metals Research School of Chemistry, University of Sydney, Sydney, 2006, Australia
SO Journal of the American Chemical Society (2003), 125(25), 7524-7525
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
AB Here the authors describe the use of x-ray absorption near edge spectroscopy (XANES) to provide information about the relative proportions of platinum(II) and platinum(IV) complexes by analyzing the XANES edge

height. The intracellular reduction of platinum(IV) complexes in cancer cells has been observed directly, and the proportion of reduction after 2 h was found to correlate with the reduction potentials of the complexes.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:228639 CAPLUS
DN 131:27016
TI Reduction of the anti-cancer drug analog cis,trans,cis-[PtCl2(OCOCH3)2(NH3)2] by L-cysteine and L-methionine and its crystal structure
AU Chen, Lie; Lee, Peng Foo; Ranford, John D.; Vittal, Jagadese J.; Wong, Siew Ying
CS Department of Chemistry, National University of Singapore, 119270, Singapore
SO Journal of the Chemical Society, Dalton Transactions: Inorganic Chemistry (1999), (8), 1209-1212
CODEN: JCDTBI; ISSN: 0300-9246
PB Royal Society of Chemistry
DT Journal
LA English
AB Cis,trans,cis-[PtCl2(OCOCH3)2(NH3)2] (1) was synthesized as a simplified and more water-soluble model of the anticancer drug cis,trans,cis-[PtCl2(OCOCH3)2(NH3)(C6H11NH2)] (JM 216). The crystal structure of 1 shows an octahedral coordination sphere around the PtIV with strong intramol. and weak intermol. H bonding. The kinetics of reduction of 1 by the divalent S amino acids L-cysteine and L-methionine was determined over a range of pH values by multinuclear NMR. The reduction is strongly pH dependent, being related to the protonation state of the amino acid and the basicity of the S. Reduction rates are dramatically slower than for previous models of Pt(IV) drug systems.
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1999:60503 CAPLUS
DN 131:279
TI Synthesis, characterization and DNA modification induced by a novel Pt(IV)-bis(monoglutarate) complex which induces apoptosis in glioma cells
AU Perez, J. M.; Camazon, M.; Alvarez-Valdes, A.; Quiroga, A. G.; Kelland, L. R.; Alonso, C.; Navarro-Ranninger, M. C.
CS Facultad de Ciencias, Departamento de Quimica Inorganica, Universidad Autonoma de Madrid, Madrid, 28049, Spain
SO Chemico-Biological Interactions (1999), 117(2), 99-115
CODEN: CBINA8; ISSN: 0009-2797
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB Programmed cell death or apoptosis is a mechanism for the elimination of cells that occurs not only in physiol. processes but also in drug-induced tumor cell death. Thus, because cisplatin, cis-diamminechloroplatinum (II), produces important damages on the DNA inducing apoptosis in several cell lines it has become a widely used antitumor drug. However, cisplatin possesses some dose-limiting toxicities mainly nephrotoxicity. Pt(IV) complexes, such as iproplatin, ormaplatin, and JM216 are a new class of platinum complexes that exhibits less toxicity than cisplatin. Some of these complexes have shown significant antitumor activity and a low cross-resistance to cisplatin. In the present paper, we have analyzed the DNA binding mode and the cytotoxicity of a novel Pt(IV)-bis(monoglutarate) complex. The data show that this novel complex produces DNA interstrand cross-links to a higher extent and with a faster kinetics

than cisplatin. Also the Pt(IV)-bis (monoglutarate) complex kills glioma cells at drug concns. significantly lower than those of cisplatin. Interestingly, this Pt(IV) complex produces in the glioma cells characteristic features of apoptosis such as 'DNA laddering' and fragmented nuclei. Moreover, the p53 protein accumulates early in glioma cells as a result of Pt(IV)-bis (monoglutarate) treatment. These data indicate that the Pt(lV)-bis (monoglutarate) complex induces apoptosis in glioma cells through a p53-dependent pathway.

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1997:683909 CAPLUS
DN 127:354661
TI Synthesis of cisplatin diacetate
AU Liu, Xinyong; Wang, Huicai; Wang, Chengyi; Tian, Jinguo; Ren, Jian
CS Dep. Pharm., Shandong Med. Univ., Jinan, 250012, Peop. Rep. China
SO Zhongguo Yiyao Gongye Zazhi (1997), 28(1), 11-12
CODEN: ZYGZEA; ISSN: 1001-8255
PB Zhongguo Yiyao Gongye Zazhi Bianjibu
DT Journal
LA Chinese
AB Cisplatin diacetate, Pt(NH3)2Cl2(OAc)2, was prepared from cisplatin by oxidation with H2O2 in acetone to give the dihydroxy precursor, followed by O-acetylation with Ac2O.

L4 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1996:121447 CAPLUS
DN 124:192389
TI Carboxylation of Dihydroxoplatinum(IV) Complexes via a New Synthetic Pathway
AU Galanski, M.; Keppler, B. K.
CS Anorganisch-Chemisches Institut, Universitaet Heidelberg, Heidelberg, D-69120, Germany
SO Inorganic Chemistry (1996), 35(6), 1709-11
CODEN: INOCAJ; ISSN: 0020-1669
PB American Chemical Society
DT Journal
LA English
AB The carboxylation of hydroxide coordinated to Pt(IV) by acyl chlorides to form the corresponding Pt(IV) carboxylates is described. Compds., Pt(IV)A2X2Y2, with A2 = diammine, ethanediamine and cis-cyclohexanediamine, X2 = dichloro, cyclobutane-1,1-dicarboxylato or malonato and Y = dodecanoato, tetradecanoato, hexadecanoato, octadecanoato, adamantanecarboxylato and acetylsalicylato, were synthesized and characterized by elemental anal., IR and NMR spectroscopic techniques. This new procedure in synthetic inorg. chemical can be transferred to a wide variety of trans-dicarboxylatoplatinum(IV) compds. which would be difficult to prepare by substitution reactions.

L4 ANSWER 20 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1992:187485 CAPLUS
DN 116:187485
OREF 116:31503a,31506a
TI Ammine/amine platinum(IV) dicarboxylates: a novel class of platinum complex exhibiting selective cytotoxicity to intrinsically cisplatin-resistant human ovarian carcinoma cell lines
AU Kelland, Lloyd R.; Murrer, Barry A.; Abel, George; Giandomenico, Christen M.; Mistry, Prakash; Harrap, Kenneth R.
CS Drug Dev. Sect., Inst. Cancer Res., Belmont/Sutton/Surrey, SM2 5NG, UK
SO Cancer Research (1992), 52(4), 822-8
CODEN: CNREA8; ISSN: 0008-5472

DT Journal
LA English
AB Using a panel of six human ovarian carcinoma cell lines varying by two orders of magnitude in terms of cisplatin cytotoxicity, the authors investigated the in vitro antitumor activity of a series of novel alkylamine ammine dicarboxylatodichloroplatinum (IV) complexes of the general formula c,t,c-[PtCl2(OCOR1)2NH3(RNH2)];R and R1= aliphatic, aromatic or alicyclic. A clear relationship existed between increasing the number of carbons in the R1 substituent and increasing cytotoxicity up to R1 = C5H11. In terms of changing the R group, maximum cytotoxic effects were conferred by alicyclic substituents. Furthermore, increasing the alicyclic ring size from cyclobutane through to cycloheptane resulted in increasing cytotoxicity. The agents with longer axial chains (e.g., JM300, R = cyclohexyl, R1 = C6H13) were more cytotoxic than cisplatin and, moreover, exhibited a selective cytotoxic effect against the most intrinsically cisplatin-resistant cell lines. The carboxylates JM221 (R = cyclohexyl, R1 = C3H7) and JM244 (R = Pr, R1 = C6H5) also retained activity against a 4-fold cisplatin-acquired resistant variant of the 41M cell line. At least part of the increased cytotoxicity of the dicarboxylate, JM221, over cisplatin appeared to be attributable to an increased intracellular accumulation. This novel class of platinum compound represents a valuable lead in the development of a "third-generation" agent capable of exhibiting activity against clin. disease currently resistant to cisplatin.

L4 ANSWER 21 OF 22 CAPLUS COPYRIGHT 2008 ACS on STN
AN 1990:584699 CAPLUS
DN 113:184699
OREF 113:31083a,31086a
TI Pt (IV) complexes as antitumor agents
IN Abrams, Michael J.; Gaindomenico, Christen M.; Murrer, Barry A.; Vollano, Jean F.
PA Johnson Matthey, Inc., USA
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | EP 328274 | A1 | 19890816 | EP 1989-300787 | 19890127 |
| | EP 328274 | B1 | 19941019 | | |
| | R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| | ES 2063119 | T3 | 19950101 | ES 1989-300787 | 19890127 |
| | IL 89119 | A | 19940412 | IL 1989-89119 | 19890130 |
| | KR 147270 | B1 | 19980817 | KR 1989-1069 | 19890131 |
| | AU 8928971 | A | 19890803 | AU 1989-28971 | 19890201 |
| | AU 618310 | B2 | 19911219 | | |
| | CA 1340286 | C | 19981222 | CA 1989-589796 | 19890201 |
| | DK 8900491 | A | 19890803 | DK 1989-491 | 19890202 |
| | DK 175050 | B1 | 20040510 | | |
| | FI 8900512 | A | 19890803 | FI 1989-512 | 19890202 |
| | FI 91260 | B | 19940228 | | |
| | FI 91260 | C | 19940610 | | |
| | NO 8900426 | A | 19890803 | NO 1989-426 | 19890202 |
| | NO 177569 | B | 19950703 | | |
| | NO 177569 | C | 19951011 | | |
| | HU 49890 | A2 | 19891128 | HU 1989-522 | 19890202 |
| | HU 205767 | B | 19920629 | | |
| | JP 01294684 | A | 19891128 | JP 1989-24751 | 19890202 |
| | ZA 8900831 | A | 19891227 | ZA 1989-831 | 19890202 |
| | US 5072011 | A | 19911210 | US 1990-602931 | 19901025 |

```
     US 5244919          A     19930914    US 1991-723971        19910701
PRAI US 1988-151674      A     19880202
     US 1989-296776      A     19890113
     US 1990-602931      A3    19901025
OS   MARPAT 113:184699
AB   Pt(IV) complexes, AA1 Pt(OCOR1)2X2 where A, A1 = NH3 or NH2, R, R1 = H,
     alkyl, alkenyl, aryl, aralykyl, alkylamino, or alkoxy or their derivs.,
     and X = halogen or alkylmono- or -dicarboxylate as antitumor agents.  Many
     of these complexes are soluble in both water and organic solvents, and this
dual
     solubility might contribute to the high antitumor activity.  Thus,
     cis-trans-cis-PtCl2(O2CH)2NH3(cyclohexylamine) was prepared by formylation
     of cis-trans-cis-PtCl2(OH)2NH3(cyclohexyl-NH2) in HCOOH during heating at
     50°.  The antitumor activity of some of these compds. was
     demonstrated and their LD50 and ED90 values (i.p. and oral) are tabulated.

L4   ANSWER 22 OF 22  CAPLUS  COPYRIGHT 2008 ACS on STN
AN   1984:582625  CAPLUS
DN   101:182625
OREF 101:27469a,27472a
TI   Study of the interaction of iminodiacetic acid with some complexes of
     platinum(IV) compounds
AU   Al-Ansari, S. V.
CS   USSR
SO   Deposited Doc. (1982), VINITI 3676-83, 344-6  Avail.: VINITI
DT   Report
LA   Russian
AB   Iminodiacetic acid (H2L) reacted with K2PtCl6, K2PtCl4(OH)2, and
     Pt(NH3)2Cl2(NO3)2 to give K[PtLCl3], K2[Pt(HL)2Cl2(OH)2], and
     Pt(HL)2(NH3)2Cl2, resp.; Pt(HL)2(NH3)2(OH)2 was also prepared  The complexes
     were characterized by IR and UV spectra, thermal decomposition studies, and
     potentiometric titrns.  The ligand is tridentate in K[PtLCl3] whereas in
     the other complexes it is monodentate.


=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    69.30     247.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -17.60     -17.60

STN INTERNATIONAL LOGOFF AT 18:51:53 ON 05 MAY 2008
```